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The [3+2] cycloaddition reaction between carbonyl ylides generated from epoxides and ketones (ethyl pyruvate, ethyl phenylglyoxylate, isatin, *N*-methylisatin and 5-chloroisatin) to give substituted dioxolanes and spirocyclic dioxolane indolinones was investigated. The effect of microwave irradiation on the outcome of the reaction was studied. The thermal reaction between 2,2-dicyano-3-phenyloxirane and *N*-methylisatin was theoretically studied using DFT methods. This reaction is a domino process that comprises two steps. The first is the thermal ring opening of the epoxide to yield a carbonyl ylide intermediate, whereas the second step is a polar [3+2] cycloaddition to yield the final spiro cycloadducts. The cycloaddition presents a low stereoselectivy and a large regio- and chemoselectivity. Analysis of the electrophilicity values and the Fukui functions at the reagents involved in the cycloaddition step allowed to explain the chemical outcome.

Introduction

Cycloaddition reactions are one of the most important synthetic processes, with both synthetic and mechanistic interest in organic chemistry. Current understanding of the underlying principles in reactions such as 1,3-dipolar cycloaddition has grown from a fruitful interplay between theory and experiment.[1] 1,3-Dipolar cycloadditions, whose general concept was introduced by Huisgen and co-workers in 1960s,[2] are versatile tools for building five-membered heterocycles.[1] Carbonyl ylides, generated by thermal electrocyclic ring opening of epoxides, are known to react with π-bonds of alkynes,[3] alkenes,[3a,b,4] imines,[5] aldehydes[6] and thioketones,[7] affording highly substituted dihydrofurans, tetrahydrofurans, oxazolidines, dioxolanes and oxathiolanes, respectively.

Spiro-oxindole system occupies a special place in heterocyclic chemistry because it is the core structure of many pharmacological agents and natural alkaloids.[8] The dioxolane moiety represents another important skeleton present in molecules endowed with biological activities,[9] notably when substituted by an aryl group at the 2 position, and both an aryl or alkyl group and an ester function at the 4 position.[10] Due to the importance of these two structural frameworks, synthesis of molecular architectures containing both spiro-oxindole and dioxolane moities could be of biological interest. We focused on spiro[1,3-dioxolane-4,3'-indolin-2'-ones], which are very rare, and have only been synthesized by Nair and co-workers using cycloadditions of carbonyl ylides generated from diazo ketones in the presence $Rh_2(OAc)_4$.[11]

To the best of our knowledge, we report here the first cycloadditions between carbonyl ylides, thermically generated from epoxides, and ketones. The mechanism of these reactions was studied using DFT calculations.

Results and discussion

Synthetic Aspects

Reactions were first carried out between 2,2-dicyano-3-(4-substituted)phenyloxiranes **1a**–**c**[12] and ethyl pyruvate (**2a**) (2 molar equivalent). The conversion to the corresponding ethyl 5,5-dicyano-4-methyl-2-phenyl-1,3-dioxolane-4-carboxylates **3**–**5** monitored by NMR showed that the reactions carried out in refluxing toluene were complete after 27 h (R = H), 29 h (R = Cl) and 14 h (R = OMe) (Table 1, Entries 1–3).

The *cis* products **3a**–**5a** were isolated from the crude mixture by column chromatography over silica gel in yields ranging from 53 to 56% and identified by NMR. NOESY, HMBC and HMQC sequences performed on a $CDCl_3$ solution of the racemic **4a** allowed the assignments of all the ^1H and ^{13}C NMR signals. In addition, the NOESY experiment clearly showed the relationship between H2 (see Table 1, **a**) at 6.27 ppm and the methyl group at C4 at 1.96 ppm. *Cis* **4a** was then identified unequivocally by X-ray structure analysis. Suitable

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† Electronic supplementary information (ESI) available: CIF files of **4a** (CCDC 654056), **7b** (CCDC 654065), **11a** (CCDC 654064), **12a** (CCDC 633367), **13a** (CCDC 654057), **14a** (CCDC 654059), **14b** (CCDC 654058), **15b** (CCDC 654060), **16a** (CCDC 654061), **17a** (CCDC 654062), **17b** (CCDC 654063) and **18b** (CCDC 654456). See http://dx.doi.org/10.1039/b000000x/

colorless crystals were obtained by slowly evaporating a $CDCl_3$ solution of **4a** (Fig. 1).† The *trans* compounds **3b**–**5b** were identified using ^1H and ^{13}C NMR spectra of enriched fractions.

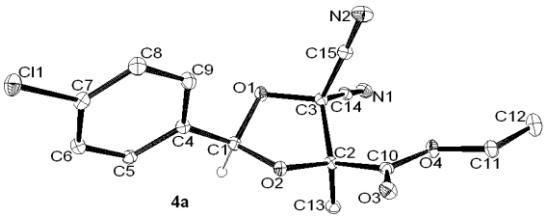


Fig. 1 ORTEP diagram (30% probability) of racemic **4a** (most of hydrogen atoms are omitted for clarity).

The diastereoisomeric ratios were determined from ^1H NMR spectra of the crude mixtures. When R = H and OMe, the *cis* products **3a** and **5a**, respectively, only slightly predominate over the *trans* products **3b** and **5b** (respective ratios of 60/40 and 59/41). When R = Cl, the formation of *cis* **4a** is slightly more favored over *trans* **4b** (64/36).

A rising number of articles have advocated the use of microwave technology in organic synthesis. Harsh conditions such as high temperatures and long reaction times often required for cycloaddition reactions could generally be reduced using this technique.[13] Syntheses of tetrahydrofurans, dioxolanes and oxazolidines using cycloaddition reactions of alkenes, aldehydes or imines with carbonyl ylides generated from epoxides were recently reported using microwave irradiation.[14]

Thus, in order to shorten the reaction times, several experiments were performed at various powers and under different conditions using microwave irradiation.[15] The best conversions were obtained without solvent (power: 285 W), with significant reduction of reaction times in comparison to reaction in toluene at reflux (55 min (R = H) against 27 h, 50 min (R = Cl) against 29 h, and 30 min (R = OMe) against 14 h). Recourse to classical heating was nevertheless preferred since the formation of the *cis* products, easier to isolate from the crude mixtures than the *trans*, was disfavored using microwave heating mode (**a**:**b** ratios of 57/43, 59/41 and 41/59 for compounds **3**–**5**, against 60/40, 64/36 and 59/41 in toluene at reflux) (Table 1, Entries 1–3).

For these reasons, reactions between 2,2-dicyano-3-(4-substituted)phenyloxiranes **1a**–**c**[12] and ethyl phenylglyoxylate (**2b**) (1 molar equivalent) were next carried out in refluxing toluene. Replacing ethyl methylglyoxylate by ethyl phenylglyoxylate slightly disfavored the formation of the *cis* compounds **6a**–**8a** over the *trans* **6b**–**8b** (**a**:**b** ratios of 54/46, 60/40 and 38/62 for compounds **6**–**8**, against 60/40, 64/36 and 59/41 for compounds **3**–**5**) (Table 1, Entries 4–6).

Whereas neither *cis* **6a** nor *trans* **6b** could be isolated as pure from the diastereoisomeric mixture but only identified using ^1H and ^{13}C NMR spectra of enriched fractions, the *cis* product **7a** and the *trans* products **7b**–**8b** were isolated from the crude mixture by column chromatography over silica gel followed by crystallization from petrol/Et_2O 4:1 in moderate to medium yields. *Trans* **8b** was identified by NMR 2D experiments. A NOESY sequence performed on a C_6D_6 solution revealed the absence of relationship between H2 (see Table 1, **b**) at 6.62 ppm and the unsubstituted phenyl *ortho* hydrogens H2" and H6" at 7.27 ppm. The structure of *trans* **7b** was elucidated by X-ray analysis of colorless crystals obtained by slowly evaporating a solution in acetone (Fig. 2).†

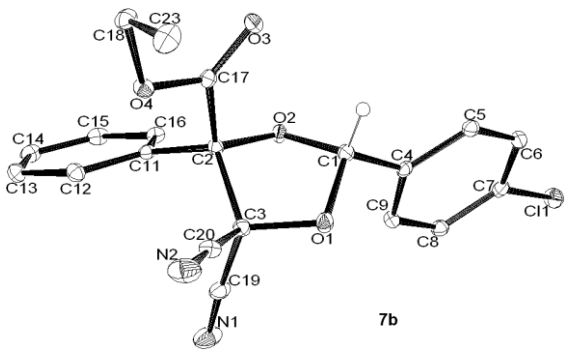
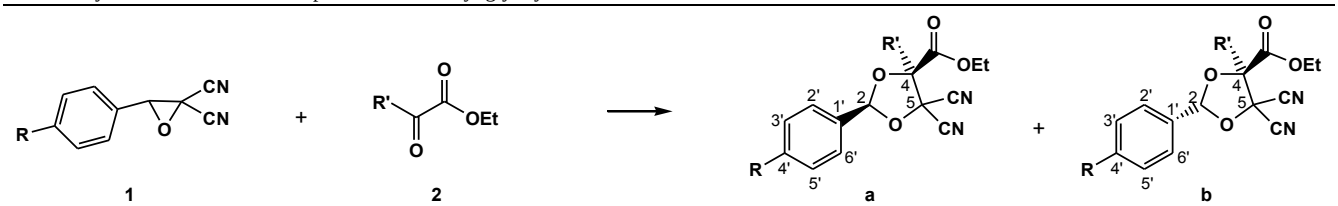


Fig. 2 ORTEP diagram (30% probability) of racemic **7b** (most of hydrogen atoms are omitted for clarity).

In order to reach spirocyclic dioxolane structures, reactions were performed with three different isatins. When carried out between 2,2-dicyano-3-phenyloxiranes **1a**–**c**[12] and isatin (**9a**) (1 molar equivalent), the reactions were completed in refluxing toluene after reaction times of 32 h (R = H), 24 h (R = Cl) and 14 h (R = OMe) to afford 5,5-dicyano-2-

Table 1 Cycloaddition reaction of epoxides **1** and ethyl glyoxylates **2**



entry	R (**1**)	R' (**2**)	**a**:**b**	**a**:**b** ratio[a,b]	**a**:**b** ratio[a,c]	**isolated product(s)**, yield(s)
1	H (**1a**)	Me (**2a**)	**3a**:**3b**	60/40	57/43	**3a**, 54%[b] (52%)[c]
2	Cl (**1b**)	Me (**2a**)	**4a**:**4b**	64/36	59/41	**4a**, 56%[b] (50%)[c]
3	OMe (**1c**)	Me (**2a**)	**5a**:**5b**	59/41	41/59	**5a**, 53%[b] (38%)[c]
4	H (**1a**)	Ph (**2b**)	**6a**:**6b**	54/46	-	-
5	Cl (**1b**)	Ph (**2b**)	**7a**:**7b**	60/40	-	**7a**, 52%; **7b**, 18%
6	OMe (**1c**)	Ph (**2b**)	**8a**:**8b**	38/62	-	**8b**, 48%

[a] Determined from the ^1H NMR spectra of the crude mixture. [b] Reactions performed in refluxing anhydrous toluene under Ar. [c] Reactions performed without solvent in a microwave oven (285 W, 180 °C).

phenylspiro[1,3-dioxolane-4,3'-indolin-2'-ones] **10**–**12** (Table 2, Entries 1–3).

The *cis* products **10a**–**12a** were isolated from the crude mixture by column chromatography over silica gel in yields ranging from 42 to 66%, and identified by NMR. NOESY, HMBC and HMQC sequences performed on the racemic **12a** allowed the assignments of all the ^{1}H and ^{13}C NMR signals. In addition, the proximity between H2 (see Table 2, **a**) at 6.41 ppm and H4' at 7.52 ppm was shown by conducting the NOESY experiment in C_6D_6. *Cis* **11a** and **12a** were then identified unequivocally by their crystal structures. Colorless crystals suitable for X-ray structure analysis were obtained by slowly evaporating an acetone solution of **11a** and a dibutyl ether solution of **12a** (Fig. 3).†

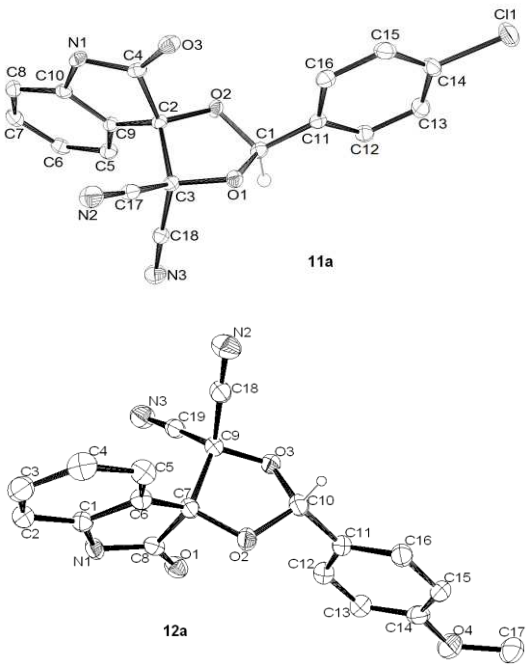


Fig. 3 ORTEP diagrams of racemic **11a** (50% probability) and **12a** (20% probability) (most of hydrogen atoms are omitted for clarity).

After identification of the *trans* compounds **10b**–**12b** using ^{1}H and ^{13}C NMR spectra of enriched fractions, the diastereoisomeric ratios were calculated from the ^{1}H NMR spectra integration of the crude mixtures. When R = H and OMe, the *cis* products **10a** and **12a**, respectively, only slightly predominate over the *trans* products **10b** and **12b** (respective ratios of 57/43 and 55/45). In contrast, when R = Cl, the formation of *cis* **11a** is clearly favored over *trans* **11b** (75/25).

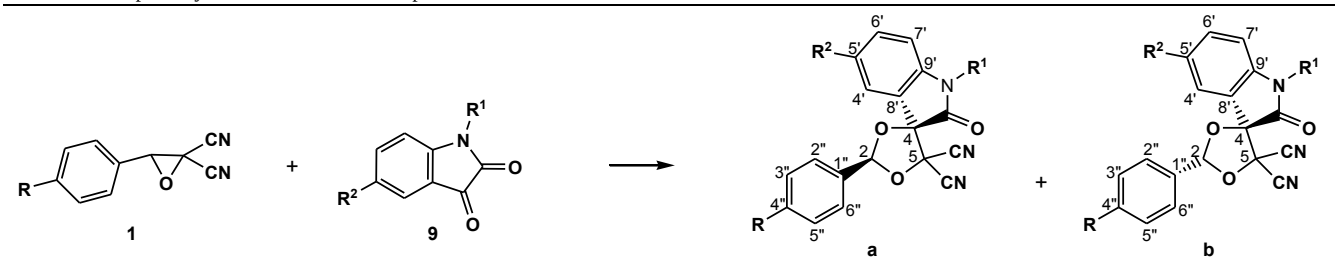
If recourse to microwave irradiation could reduce the reaction times as previously noted, it was again discarded, the formation of the *trans* products, more difficult to isolate for the crude mixtures than the *cis*, being similarly favored using this heating mode (Table 2, Entries 1–3).

The reactions carried out between 2,2-dicyano-3-phenyloxiranes **1a**–**c**[12] and *N*-methylisatin (**9b**) (0.7 molar equivalent) in refluxing toluene show that the methyl group on isatin helps in favoring the formation of the *cis* products. Indeed, diastereoisomeric ratios of 73/27, 74/26 and 63/37 were respectively obtained for compounds **13**–**15** against 57/43, 75/25 and 55/45 for compounds **10**–**12** (Table 2, Entries 4–6).

The *cis* products **13a** and **14a** were isolated from the crude mixture by fractional crystallization from petrol/Et_2O 5:1 in satisfying yields. *Cis* **13a** was identified from its ^{1}H and ^{13}C NMR spectra. After complete assignments of all the ^{1}H and ^{13}C signals using NOESY, HMBC and HMQC sequences performed on **14a**, the proximity between H2 (see Table 2, **a**, 6.98 ppm) and H4' (7.86 ppm) was evidenced using the NOESY spectrum. The structures of **13a** and **14a** were confirmed by X-ray analysis of colorless crystals obtained by slowly evaporating an acetone solution (Fig. 4).†

Cis **15a** could not be purified, but *trans* **15b** was isolated in 30% yield, and its structure elucidated by X-ray analysis. Single crystals of *trans* **14b** suitable for X-ray diffraction

Table 2 1,3-Dipolar cycloaddition reaction of epoxides **1** and isatins **9**.



entry	R (**1**)	R^1, R^2 (**9**)	**a**:**b**	**a**:**b** ratio[a,b]	**a**:**b** ratio[a,c]	**isolated product(s)**, yield(s)
1	H (**1a**)	H, H (**9a**)	**10a:10b**	57/43	55/45	**10a**, 42%[b]
2	Cl (**1b**)	H, H (**9a**)	**11a:11b**	75/25	54/46	**11a**, 66%[b]
3	OMe (**1c**)	H, H (**9a**)	**12a:12b**	55/45	35/65	**12a**, 49%[b]
4	H (**1a**)	Me, H (**9b**)	**13a:13b**	73/27	-	**13a**, 72%
5	Cl (**1b**)	Me, H (**9b**)	**14a:14b**	74/26	-	**14a**, 73%
6	OMe (**1c**)	Me, H (**9b**)	**15a:15b**	63/37	-	**15b**, 30%
7	H (**1a**)	H, Cl (**9c**)	**16a:16b**	59/41	-	**16a**, 52%; **16b**, 28%
8	Cl (**1b**)	H, Cl (**9c**)	**17a:17b**	71/29	-	**17a**, 59%; **17b**, 25%
9	OMe (**1c**)	H, Cl (**9c**)	**18a:18b**	58/42	-	**18a**, 49%

[a] Determined from the ^{1}H NMR spectra of the crude mixture. [b] Reactions performed in refluxing anhydrous toluene under Ar. [c] Reactions performed without solvent in a microwave oven (285 W, 180 °C).

analysis were collected too (Fig. 5).† The products **15a** and **13b** were identified using ^{1}H and ^{13}C NMR spectra of enriched fractions.

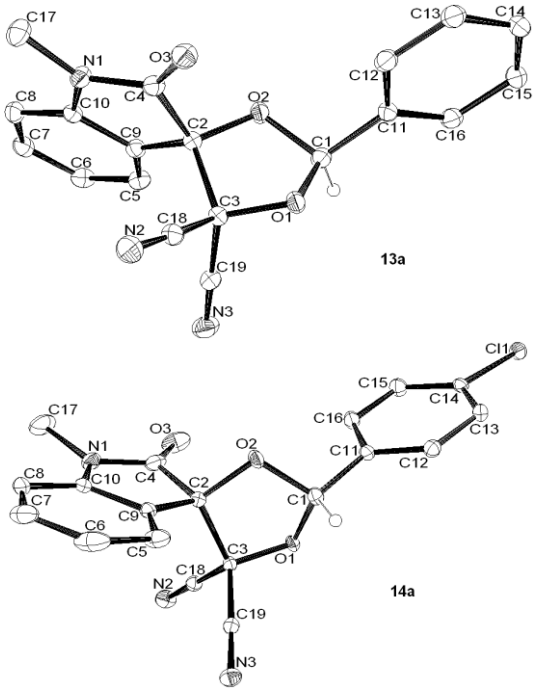


Fig. 4 ORTEP diagrams (30% probability) of racemic **13a** and **14a** (most of hydrogen atoms are omitted for clarity).

The presence of a chloro group at the 5-position of isatin does not greatly affect the diastereoisomeric ratios. Indeed, when 5-chloroisatin (**9c**) (0.7 molar equiv) was similarly involved in the reactions with 2,2-dicyano-3-phenyloxiranes **1a**–**c**,[12] **a**:**b** ratios of 59/41, 71/29 and 58/42 were respectively obtained for compounds **16**–**18**, against 57/43, 75/25 and 55/45 using isatin (**9a**) (Table 2, Entries 7–9).

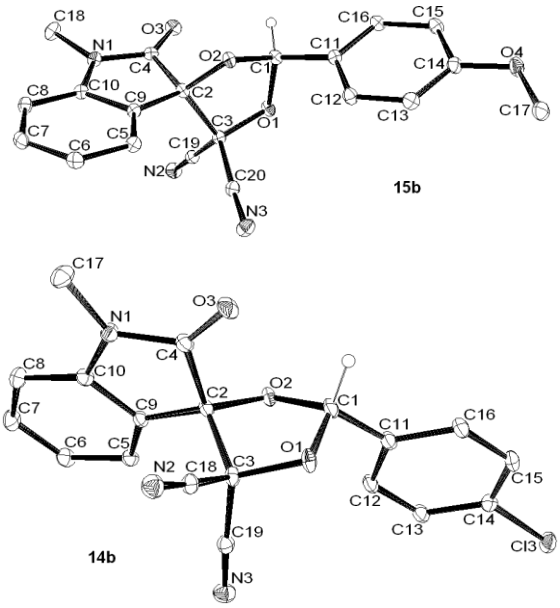


Fig. 5 ORTEP diagrams (30% probability) of racemic **15b** and **14b** (most of hydrogen atoms are omitted for clarity).

The products **16a**, **17a**, **18a**, **16b** and **17b** were isolated from the crude mixtures by fractional crystallization from CH_2Cl_2. Concerning **18b**, only single crystals suitable for X-ray diffraction analysis were collected. The X-ray structures obtained from colorless crystals of **16a**, **17a**, **17b** and **18b** (Fig. 6)† (slowly evaporation of acetone solutions) are consistent with the interpretation of the NMR spectra.

Calculations: Theoretical study of the domino reaction between the epoxide **1a** and the isatin **9b**.

The thermal cycloaddition reaction between the epoxide **1a** and the isatin **9b** to yield the spiro-cycloadducts **13a**,**b** is a domino process that comprises two consecutive reactions: i) the thermal ring opening of **1a** through the breaking of the C-

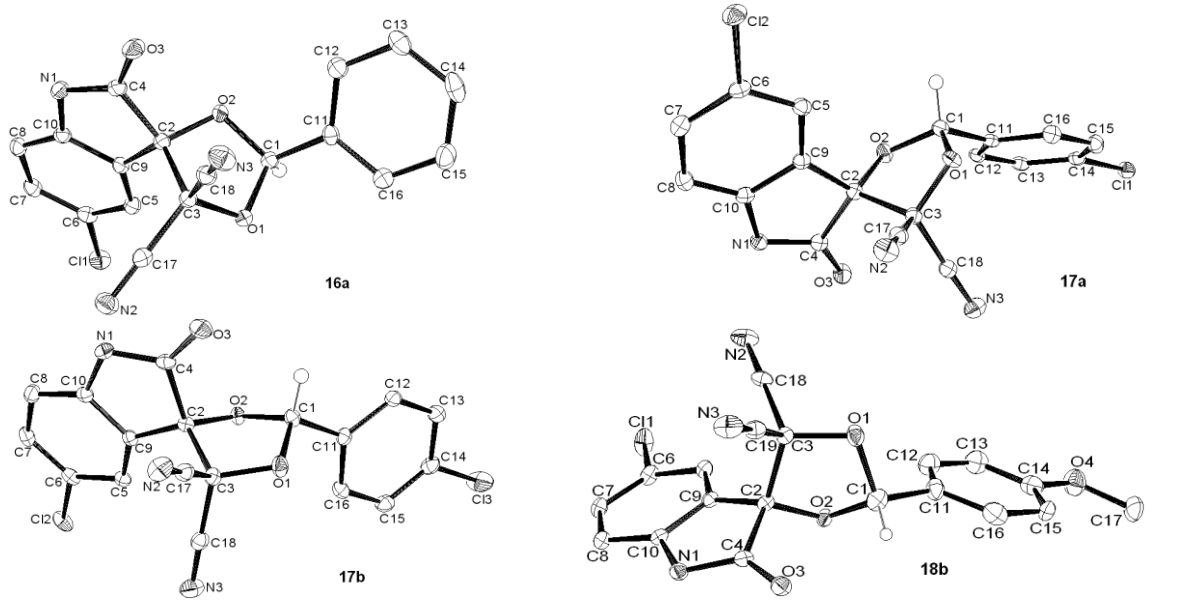
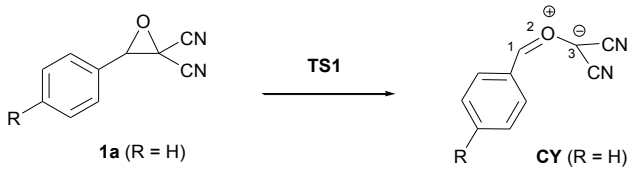
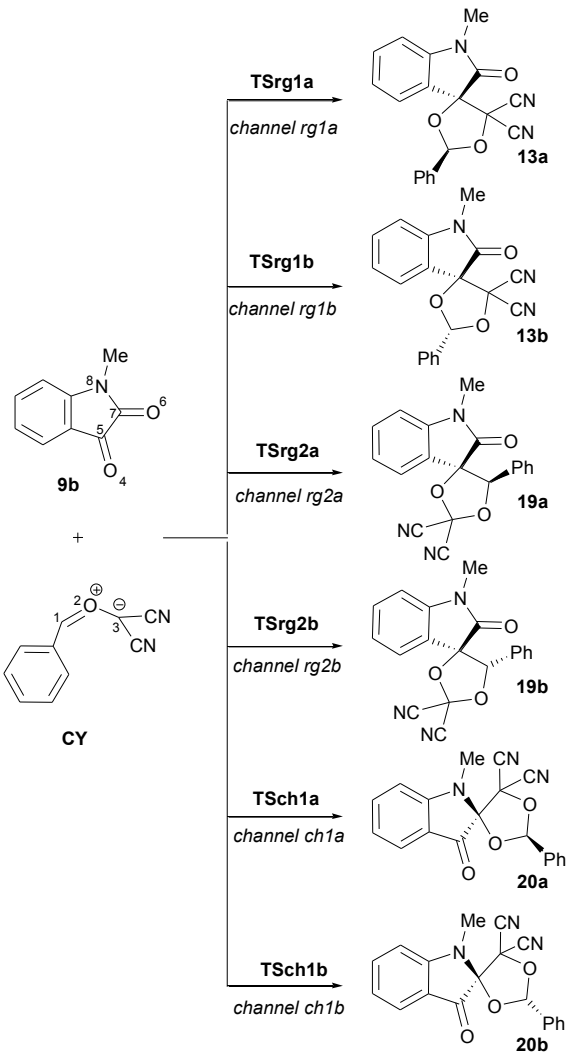


Fig. 6 ORTEP diagrams of racemic **16a**, **17a**, **17b** (50% probability) and **18b** (30% probability) (most of hydrogen atoms are omitted for clarity).

C bond to yield the carbonyl ylide intermediate **CY**, and ii) a [3+2] cycloaddition reaction between **CY** and the isatin **9b**. In order to obtain mechanistic details as well as the stereo-, regio- and chemoselectivity of the formation of the spirocyclic dioxolane indolinones **13a**,**b** (see Schemes 1 and 2), the two steps involved in these domino reactions were studied using DFT calculations at the B3LYP/6-31G* level.



Scheme 1 Thermal ring opening of the epoxide **1a**.



Scheme 2 Cycloaddition reaction between **CY** and the isatin **9b**.

*Study of the thermal ring opening of the epoxide **1a**.*

The first step of this domino reaction is the thermal ring opening of the epoxide **1a** through the breaking of the C1-C3 bond of the oxirane to yield the carbonyl ylide intermediate **CY**. An exhaustive exploration of the reaction path of this step allowed to find a transition structure, **TS1**, and the subsequent carbonyl ylide **CY** (see Scheme 1).

In gas phase, the activation energy associated to the breaking of the C1-C3 bond of the epoxide **1a** is 26.9 kcal mol^{-1}; the carbonyl ylide **CY** is located 11.7 kcal mol^{-1} above the epoxide **1a** (see Table 3). These highly unfavorable energies are in reasonable agreement with the high temperature required for the reaction (toluene at reflux).

The geometry of **TS1** is given in Fig. 7. The length of the C1-C3 breaking bond at **TS1** is 2.124 Å. Analysis of the atomic movement associated to the unique imaginary frequency of **TS1**, 112.9i cm^{-1}, shows that this TS is mainly associated to the C1-C3 breaking bond and to the disrotatory movement of the substituents present at these carbon atoms, as a consequence of the change in the hybridization of C1 and C3 carbon atoms from sp^3 in **1a** to sp^2 in **CY**. The carbonyl ylide **CY** presents a planar rearrangement that allows the maximum stabilization by charge delocalization at the corresponding zwitterionic structure. The C1-O2 bond length in **CY** is very short, 1.294 Å, as a consequence of the delocalization of the O2 oxygen lone pair over the C1 carbon. On the other hand, both C3-CN bond lengths at **CY**, 1.400 Å, are shorter than those at the epoxide **1a**, 1.455 Å, as a consequence of the delocalization of the negative charge present on C3 towards the two electron-withdrawing CN groups.

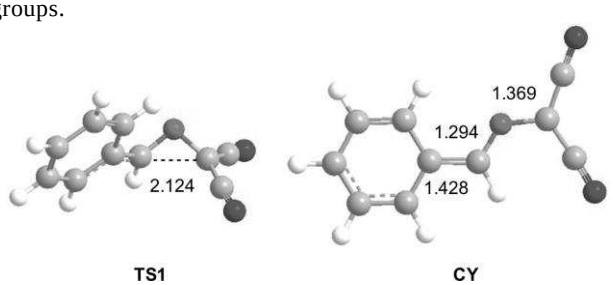


Fig. 7 Geometry of **TS1** and the carbonyl ylide **CY**. The bond lengths are given in angstroms.

The extent of bond formation and bond rupture along the reaction pathway is provided by the concept of bond order (BO).[16] At **TS1**, the BO value of the C1-C3 breaking bond is 0.31. This low value indicates that, at the TS, the breaking bond process is very advanced. This fact is in clear agreement with the endothermic character of the process.[17] At the carbonyl ylide **CY**, the C1-O2 BO value, 1.24, points out its π character as a consequence of some delocalization of the O2 oxygen lone pair over the C1 carbon. The C1-C(Ar) bond order value, 1.22, indicates the participation of the π aromatic ring in the stabilization of the carbonyl ylide. On the other hand, the BO value of both C3-C(CN) bonds, 1.17, points out their π character as a consequence of the delocalization of the negative charge developed over the C3 carbon atom over the two electron-withdrawing CN groups.

*Study of the [3+2] cycloaddition reaction of the carbonyl ylide **CY** with the isatin **9b**.*

Due to the existence of two C=O reactive centers at the isatin **9b**, a carbonyl C5-O4 and an amide carboxyl C7-O6 double bond, and the asymmetry of both reagents, this cycloaddition reaction can yield up to eight isomeric spiro-cycloadducts.

The formation of these cycloadducts can be related to the chemo-, regio- and stereoselectivity of this cycloaddition reaction. The experimental results indicate that these cycloaddition reactions take place with a total chemoselectivity, with the unique participation of the carbonyl C5-O4 double bond, with total regioselectivity, with the unique formation of the regioisomers associated to the C1-O4 and C3-C5 bond formation, and with a low stereoselectivity due to the formation of the two possible stereoisomers. In order to explain the experimental results, the chemo-, regio- and stereoselectivity associated to these cycloadditions were studied. For this purpose we studied: the two stereoselective channels associated to the approach of the carbonyl ylide O2 oxygen atom to the plane containing the C=O π bond, named as *a* and *b*; those regioisomeric channels associated to the approach of carbonyl ylide **CY** to the carbonyl C5-O4 double bond of **9b**, named as channels *rg1* and *rg2*, and finally, the more favorable regioisomeric approach modes of **CY** to the carboxyl C7-O6 double bond of **9b**, named as channels *ch1*, allowed us to study the chemoselectivity in these cycloaddition reactions. Therefore, six reactive channels were studied (see Scheme 2). An exhaustive exploration of the potential energy surface of these cycloadditions allowed us to find a series of molecular complexes (MCs) that open the cycloaddition pathways. In these MCs, the two reagents are separated by 2.8 Å. From these MCs we selected the more favorable one, **MC**. **MC** is located –7.1 kcal mol^{-1} below reagents, **CY** + **9b**. Analysis of the stationary points involved in these cycloaddition reactions indicates that they present concerted mechanisms. Hence, six TS, **TSrg1a**, **TSrg1b**, **TSrg2a**, **TSrg2b**, **TSch1a**, and **TSch1b**, and the corresponding spiro-cycloadducts were located and characterized.

The energy results are summarized in Table 3. The most favorable reactive channels correspond to the formation of the stereoisomeric spiro-cycloadducts **13a** and **13b**, via **TSrg1a** and **TSrg1b**, respectively. From **MC**, the activation energies associated to the formation of the spiro-cycloadducts **13a** and **13b** are 5.5 (**TSrg1a**) and 6.5 (**TSrg1b**) kcal mol^{-1}**.** The low energy difference between **TSrg1a** and **TSrg1b**, ΔΔE = 1.0 kcal mol^{-1}, agrees with the low stereoselectivity experimentally observed. Note that major stereoisomer **13a** has the *cis* stereochemistry. **TSrg2a** and **TSrg2b**, are located *ca*. 10 kcal mol^{-1} above **TSrg1a**. This large energy difference prevents the formation of the regioisomeric cycloadducts **19a** and **19b**, fact that is consistent with the experimental results. Finally, the formation of the spiro-cycloadduct **20a**, via **TSch1a**, is 2.9 kcal mol^{-1} more unfavorable than the formation of **13a**. This energy result is in reasonable agreement with the chemoselectivity experimentally observed (attack to the carbonyl C5-O4 double bond against the attack to the carboxyl C7-O6 one). The chemoselectivity can be explained by a larger nucleophilic character of the carbonyl O6 oxygen than the carboxyl O6 oxygen (see later). All these cycloaddition reactions are strongly exothermic: between –29 and –32 kcal mol^{-1} for the *rg1* and *rg2* regioisomeric channels and between –19 and –20 kcal mol^{-1} for the *ch1* regioisomeric channels.

The geometries of the TSs involved in these cycloadditions are given in Fig. 8. The lengths of the forming bonds at the TSs are: 1.966 Å (C1-O4) and 2.425 Å (C3-C5) at **TSrg1a**, 2.007 Å (C1-O4) and 2.614 Å (C3-C5) at **TSrg1b**, 2.036 Å (C3-O4) and 2.209 Å (C1-C5) at **TSrg2a**, 2.061 Å (C3-O4) and 2.176 Å (C1-C5) at **TSrg2b**, 1.913 Å (C1-O6) and 2.687 Å (C3-C7) at **TSch1a** and 1.801 Å (C1-O6) and 2.551 Å (C3-C7) at **TSch1b**. Some conclusions can be drawn from these values: i) at all TSs, the length of the O-C forming bond is shorter that the C-C one, and ii) the more favorable regioisomeric TSs, *rg1*, are more asynchronous than the regioisomeric *rg2* ones. Note that the *ch1* channels are equivalent to the *rg1* ones.

Table 3 Total (E, in au) and relative[a] (ΔE, in kcal mol^{-1}) energies, and total (G_{sol}, in au) and relative[a] (ΔG_{sol}, in kcal mol^{-1}) free energies in toluene at 383.95 K, of the stationary points involved in the cycloaddition reaction between the carbonyl ylide **1a** and the isatin **9b**.

	E	ΔE	G_{sol}	ΔG_{sol}
1a	-569.307603		-569.238018	
9b	-552.378472		-552.296654	
TS1	-569.264771	26.9	-569.200802	23.4
CY	-569.289033	11.7	-569.224206	8.7
CM	-1121.678679	4.6	-1121.504526	18.9
TSrg1a	-1121.670024	10.1	-1121.486682	30.1
TSrg1b	-1121.668391	11.1		
TSrg2a	-1121.651633	21.6	-1121.468107	41.8
TSrg2b	-1121.652029	21.4		
TSch1a	-1121.665334	13.0	-1121.482218	32.9
TSch1b	-1121.663287	14.3		
13a	-1121.716275	-19.0	-1121.527140	4.7
13b	-1121.718022	-20.0		
19a	-1121.714572	-17.9	-1121.526722	5.0
19b	-1121.713157	-17.0		
20a	-1121.698900	-8.0	-1121.512390	14.0
20b	-1121.697709	-7.3		

[a] Energies relative to **1a** + **9b**.

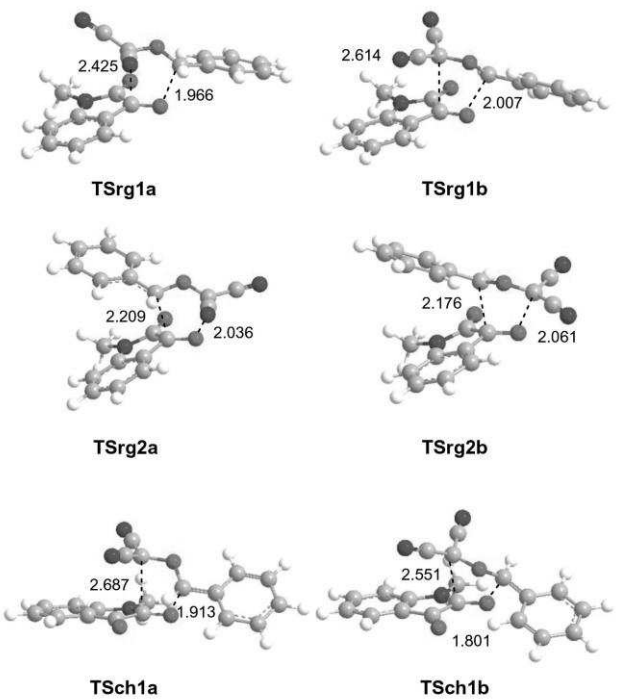


Fig. 8 Geometry of the TSs involved in the cycloaddition reactions between the carbonyl ylide **CY** and the isatin **9a**. The bond lengths are given in angstroms.

The BO values of the forming bonds at these TSs are: 0.34 (C1-O4) and 0.22 (C3-C5) at **TSrg1a**, 0.31 (C1-O4) and 0.17 (C3-C5) at **TSrg1b**, 0.32 (C3-O4) and 0.34 (C1-C5) at **TSrg2a**, 0.31(C3-O4) and 0.34 (C1-C5) at **TSrg2b**, 0.37 (C1-O6) and 0.12 (C3-C7) at **TSch1a**, and 0.46 (C1-O6) and 0.16 (C3-C7) at **TSch1b**. These BO values indicate that both regioisomeric series of TSs present a different behavior. While the TSs associated to the *rg1* channel, including the *ch1* one, correspond to asynchronous bond-formation processes where the formation of the C-O bond is more advanced than the C-C one, the more unfavorable TSs associated to the *rg2* channel correspond to synchronous bond-formation processes where the C-C bond formation is slightly more advanced than the C-O one.

The natural population analysis (NPA) allows us to evaluate the charge separation at the TSs, that is the polar character of the cycloaddition. The natural charges at the TSs appear shared between the carbonyl ylide **CY**, and the isatin **9b**. The net charge at the isatin **9b** framework at the TSs are: –0.09 e at **TSrg1a**, –0.13 e at **TSrg1b**, –0.26 e at **TSrg2a**, –0.25 e at **TSrg2b**, 0.0 e at **TSch1a** and –0.01 e at **TSch1b**. These values indicate that at the TSs associated to the attack of the carbonyl C5-O4 double bond there is some charge separation, and that it is larger at the more unfavorable regioisomeric TSs. At the TSs associated to the attack of the carboxyl C7-O6 double bond, the charge separation is unappreciable.

*Thermodynamic analysis of the domino reaction between **1a** and **9b**.*

As the two reactions involved in this domino process present different molecularity: the ring-opening process is unimolecular and the cycloaddition reaction is bimolecular, the free energies of the stationary points associated to the stereoisomeric channels ***a*** were computed at 383.95 K. Solvent effects of toluene on the energies were considered at the thermodynamic calculations (see computational methods). The energy results are summarized in Table 3, while a schematic representation of the free energy profiles is depicted in Fig. 9.

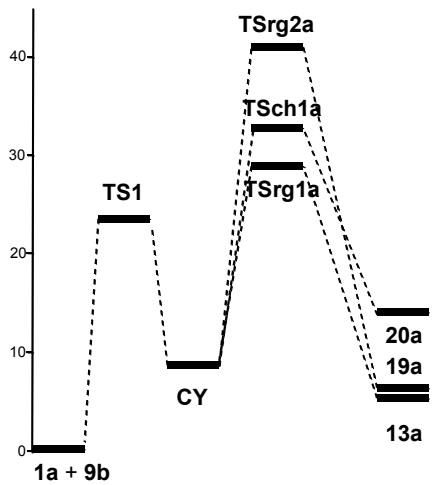


Fig. 9 Free energy profiles, in kcal mol^{-1}, for the domino reaction between the epoxide **1a** and the isatin **9b**.

The activation free energy (considering the solvent effects) associated to the ring-opening process is 23.4 kcal mol^{-1}. Formation of the carbonyl ylide **CY** is an endergonic process in 8.7 kcal mol^{-1}. Two factors are responsible of the decrease of these unfavorable energies respect to the gas-phase results: i) solvent effects stabilize more efficiently the **TS1** and the carbonyl ylide **CY** than the epoxide **1a** as a consequence of the zwitterionic character of the formers, and ii) an increase of the entropy of the system along the ring opening process.

The inclusion of solvent effects and thermal corrections to the energies and the entropies rises the relative free energies of the stationary points involved in the [3+2] cycloaddition reactions as a consequence of the bimolecular character of the reactions. Now **MC** is located 10.2 kcal above reagents, **CY** + **9b**. Therefore, in spite of the exothermic character of the formation of **MC**, its existence on the free energy surface is irrelevant. The free activation energy associated to **TSrg1a** is 20.0 kcal mol^{-1} (relative to **CY** + **9b**). **TSrg2a** remains 11.7 kcal mol^{-1} above **TSrg1a**, so this regioisomeric channel is clearly unfavorable. Although the chemoselectivity, measured as $\Delta\Delta G^{\#}$, decreases slightly to 2.8 kcal mol^{-1}, the formation of **13a** is exergonic in –3.9 kcal mol^{-1} and the formation of **20a** is endergonic in 5.3 kcal mol^{-1}.

Both ring opening and cycloaddition reactions have similar activation energies but, due to the endergonic character of the formation of **CY**, **TSrg1a** is located 6.8 kcal mol^{-1} above **TS1** and, therefore, the cycloaddition reaction becomes the rate-determining step of this domino process. In addition, the overall process is endergonic in 4.7 kcal mol^{-1}.

Analysis based in the reactivity indexes.

Recent studies carried out on cycloaddition reactions[18] have shown that the reactivity indexes[19] are powerful tools to study the reactivity. In Table 4, the static global properties (electronic chemical potential, μ, chemical hardness, η, and global electrophilicity, ω) of the carbonyl ylides **CY** (R = H) and **CY'** (R = OMe), and isatins **9a,b**, are presented.

Table 4 Electronic chemical potential, μ in au, chemical hardness, η in au, and global electrophilicity, ω in eV, for the carbonyl ylides **CY** and **CY'** and the isatins **9a,b**.

	μ(au)	η(au)	ω(eV)
CY (R = H)	-0.1693	0.0908	4.29
CY' (R = OMe)	-0.1576	0.0890	3.79
9a (R^1 = R^2 = H)	-0.1691	0.1433	2.71
9b (R^1 = Me, R^2 = H)	-0.1646	0.1385	2.66

The electronic chemical potential of the carbonyl ylides **CY** and **CY'**, –0.1693 and –0.1576 au, are close to those of the isatins **9a,b**, –0.1691 and –0.1646 au. The presence of electron-releasing substituents, methyl or methoxy, increases the value of the electronic chemical potential of these molecules. The similar values found in these reagents do not allow to predict clearly the direction of the charge transfer along these polar cycloadditions.

The carbonyl ylides present a very large electrophilicity value, 4.29 (**CY**) and 3.79 (**CY'**) eV, being classified as strong electrophiles within the electrophilicity scale.[18] The inclusion of an electron-releasing methoxy group on the aryl substituent decreases slightly the electrophilicity of the

carbonyl ylide. The electrophilicity value of the isatin **9a** (R^1 = R^2 = H) is 2.71 eV, being also classified also as a strong electrophile. Inclusion of an electron-releasing methyl group on the amide nitrogen atom decreases slightly the electrophilicity value of isatin **9b** (R^1 = Me, R^2 = H) to 2.66 eV. This decrease with the electron-releasing substitution, which can be related with an increase of the nucleophilicity of this compound, is in agreement with the reduction of the reaction time for isatin **9b** relative to that for isatin **9a**.

The larger electrophilicity values of the carbonyl ylides **CY** and **CY'** respect to the isatins **9a,b** indicate that, along a polar cycloaddition, the carbonyl ylides **CY** and **CY'** will behave as electrophiles whereas the isatins **9a,b** will behave as nucleophiles.[20]

Analysis of the Fukui functions at the carbonyl ylide **CY** indicates that the C1 carbon corresponds to the most electrophilic center of this intermediate, while its C3 carbon is the most nucleophilic center. This picture agrees with a heterolytic C-C bond breaking along the ring-opening process, where the negative charge on the C3 carbon is delocalized over the two adjacent electron-withdrawing cyano groups, while the positive charge developed on the C1 carbon is stabilized by the O2 oxygen and the nearby conjugated phenyl substituent. On the other hand, at the isatin **9b**, while the carbonyl C5 carbon atom is the most electrophilic center, the carbonyl O4 oxygen atom is the most nucleophilic one. In a polar cycloaddition, the more favorable electronic interaction takes place between the most electrophilic center of the electrophile reagent and the most nucleophilic center of the nucleophile reagent. This favorable electronic interaction controls both the asynchronicity of the bond formation and the regioselectivity of the reaction. Therefore, both the asynchronicity found at the TSs as well as the regioselectivity of the reactions are in agreement with the electrophile/nucleophile interaction predicted by the analysis of the Fukui functions.

Conclusions

In conclusion, we have shown that first ethyl 4-phenyl or 4-methyl-2-phenyl-1,3-dioxolane-4-carboxylate and then 2-phenylspiro[1,3-dioxolane-4,3'-indolin-2'-ones] can be easily prepared by a regioselective cycloaddition between ethyl glyoxylates or isatins, and carbonyl ylides, thermically generated from epoxides. It is relevant to mention that *trans* spiro[1,3-dioxolane-4,3'-indolin-2'-ones] have been synthesized by Nair and co-workers using carbonyl ylides generated from diazo ketones in the presence of $Rh_2(OAc)_4$,[11] whereas our method rather favors the formation of *cis* products, which are unknown.

The cycloaddition reaction between 2,2-dicyano-3-phenyloxirane and *N*-methylisatin to yield spiro-cycloadducts has been theoretically studied using DFT methods at the B3LYP/6-31G* level. The reaction is a domino process that comprises two steps. The first one is the thermal cleavage of the oxirane ring to yield a carbonyl ylide intermediate, whereas the second step is a [3+2] polar cycloaddition initialized by the nucleophilic attack of *N*-methylisatin to the carbonyl ylide to yield final spiro-cycloadducts. Spite of the large activation energy associated to the oxirane cleavage and the low activation energy associated to the subsequent nucleophilic attack, thermodynamic calculations in toluene indicate that the cycloaddition reaction is the rate-determining step. The cycloaddition presents a low stereoselectivy and a large regio- and chemoselectivity. The more favorable channels are associated to the nucleophilic attack of the isatin carbonyl oxygen atom to the phenyl substituted carbon atom of the carbonyl ylide.

Analysis of the reactivity indexes of the reagents indicates that while the large electrophilicity of the carbonyl ylide accounts for the nucleophilic attack of isatin to ylide, analysis of the Fukui functions allows to explain the regio- and chemoselectivity experimentally observed. The more favorable electronic interaction takes place between the carbonyl oxygen atom of isatin, the more nucleophilic center, and the phenyl substituted carbon atom of the carbonyl ylide, the more electrophilic one.

Experimental

Syntheses: general methods

Melting points were measured on a Kofler apparatus. NMR spectra were recorded with a Bruker ARX 200P, a Bruker Avance 300P or a Bruker Avance 300M spectrometer (^{1}H at 200 or 300 MHz, and ^{13}C at 50 or 75 MHz). Assignments of protons and carbons could be made on the basis of bidimensional techniques (NOESY, HMQC and HMBC experiments). Mass spectra (HRMS) were recorded with a Varian MAT 311 spectrometer, and microanalyses were performed on a Flash EA1112 Thermo Electron. Microwave reactions were performed in open glass containers (Prolabo Synthewave® 402) with accurate control of power (maximum power: 300 W) and temperature (infrared detection).

Oxiranes were prepared according to described procedures.[12] Toluene was dried before use. Reactions were performed under dry argon. Petrol refers to petroleum ether (bp 40–60°C).

General procedure 1. A mixture of epoxide (3 mmol) and ketone (amount given in the product description) in anhydrous toluene (30 mL) was heated at reflux under Ar. The mixture was then evaporated to dryness and purified as specified in the product description.

General procedure 2. A mixture of epoxide (3 mmol) and ketone (amount given in the product description) was heated in a microwave oven (power, temperature and time are given in the product description). The residue was purified as specified in the product description.

Diastereoisomers of ethyl 5,5-dicyano-4-methyl-2-phenyl-1,3-dioxolane-4-carboxylate (3). The general procedure 1 (reflux of 27 h), using 3-phenyloxirane-2,2-dicarbonitrile (**1a**, 0.51 g) and ethyl pyruvate (**2a**, 0.70 g, 0.66 mL, 6.0 mmol), gave a 60/40 mixture from which the major diastereoisomer **3a** was isolated by column chromatography over silica gel (eluent: petrol/AcOEt 70:30) in 54% (0.46 g) yield as a greenish oil: ^{1}H NMR ($CDCl_3$): δ 1.41 (t, 3H, *J*=7.1 Hz, CH_3), 1.97 (s, 3H, CH_3), 4.37-4.47 (m, 2H, CH_2), 6.29 (s, 1H, H2), 7.42-7.57 (m, 5H, Ph); ^{13}C NMR

($CDCl_3$): δ 14.0 (CH_3CH_2), 19.5 (CH_3), 63.9 (CH_2), 70.3 (C5), 88.8 (C4), 107.5 (C2), 110.8 (CN), 112.0 (CN), 127.4 and 129.0 (C2', C3', C5' and C6'), 131.2 (C4'), 132.7 (C1'), 166.1 (C=O); HRMS, *m/z*: 286.0961 and 213.0666 found (calcd for $C_{15}H_{14}N_2O_4$, $M^{+\bullet}$, and $C_{12}H_9N_2O_2$, $[M\text{-}CO_2Et]^{+\bullet}$, requires: 286.09536 and 213.06640, respectively). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 63.15; H, 5.09; N, 9.68%. The minor diastereoisomer **3b** was identified by NMR: ^{1}H NMR ($CDCl_3$): δ 1.42 (t, 3H, *J*=7.1 Hz, CH_3), 1.98 (s, 3H, CH_3), 4.42 (q, 2H, *J*=7.1 Hz, CH_2), 6.50 (s, 1H, H2), 7.43-7.58 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 13.9 (CH_3CH_2), 21.5 (CH_3), 63.8 (CH_2), 71.4 (C5), 88.4 (C4), 108.5 (C2), 110.9 (CN), 111.1 (CN), 127.1 and 128.8 (C2', C3', C5' and C6'), 131.1 (C4'), 132.9 (C1'), 167.1 (C=O). The general procedure 2 (285 W, 15 min to reach 180°C and 55 min at 180°C), using 3-phenyloxirane-2,2-dicarbonitrile (**1a**, 0.51 g) and ethyl pyruvate (**2a**, 0.46 g, 0.44 mL, 4.0 mmol), gave a 57/43 mixture from which the major diastereoisomer **3a** was isolated by column chromatography over silica gel (eluent: petrol/AcOEt 70:30) in 52% (0.45 g) yield.

Diastereoisomers of ethyl 2-(4-chlorophenyl)-5,5-dicyano-4-methyl-1,3-dioxolane-4-carboxylate (4). The general procedure 1 (reflux of 29 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.61 g) and ethyl pyruvate (**2a**, 0.70 g, 0.67 mL, 6.0 mmol), gave a 64/36 mixture from which the major diastereoisomer **4a** was isolated by column chromatography over silica gel (eluent: petrol/AcOEt 50:50) in 56% (0.54 g) yield as a pale yellow glitter: mp 86°C; ^{1}H NMR ($CDCl_3$): δ 1.40 (t, 3H, *J*= 7.1 Hz, CH_3), 1.96 (s, 3H, CH_3), 4.39-4.47 (m, 2H, CH_2), 6.27 (s, 1H, H2), 7.43 (d, 2H, *J*=8.5 Hz, H3' and H5'), 7.50 (d, 2H, *J*=8.6 Hz, H2' and H6'); ^{13}C NMR ($CDCl_3$): δ 13.7 (CH_3CH_2), 19.1 (CH_3), 63.7 (CH_2), 70.0 (C5), 88.7 (C4), 106.4 (C2), 110.5 (CN), 111.8 (CN), 128.6 (C2' and C6'), 129.0 (C3' and C5'), 131.2 (C1'), 137.0 (C4'), 165.8 (C=O); HRMS, *m/z*: 320.0557 and 247.0265 found (calcd for $C_{15}H_{13}N_2O_4{}^{35}Cl$, $M^{+\bullet}$, and $C_{12}H_8N_2O_2{}^{35}Cl$, $[M\text{-}CO_2Et]^{+\bullet}$, requires: 320.05638 and 247.02743, respectively). Anal. Calcd for $C_{15}H_{13}ClN_2O_4$: C, 56.17; H, 4.09; N, 8.73. Found: C, 56.35; H, 4.17; N, 8.63%. The minor diastereoisomer **4b** was identified by NMR: ^{1}H NMR ($CDCl_3$): δ 1.42 (t, 3H, *J*= 7.1 Hz, CH_3), 1.96 (s, 3H, CH_3), 4.42 (q, 2H, *J*=7.2 Hz, CH_2), 6.47 (s, 1H, H2), 7.44 (s, 4H, Ph); ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3CH_2), 21.5 (CH_3), 64.0 (CH_2), 71.4 (C5), 88.5 (C4), 107.8 (C2), 110.8 (CN), 111.0 (CN), 128.5 and 129.3 (C2', C3', C5' and C6'), 131.5 (C1'), 137.2 (C4'), 167.0 (C=O). The general procedure 2 (285 W, 15 min to reach 180°C, and 50 min at 180°C), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.61 g) and ethyl pyruvate (**2a**, 0.46 g, 0.44 mL, 4.0 mmol), gave a 59/41 mixture from which the major diastereoisomer **4a** was isolated by column chromatography over silica gel (eluent: petrol/AcOEt 50:50) in 50% (0.48 g) yield.

Diastereoisomers of ethyl 5,5-dicyano-2-(4-methoxyphenyl)-4-methyl-1,3-dioxolane-4-carboxylate (5). The general procedure 1 (reflux of 14 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.60 g) and ethyl pyruvate (**2a**, 0.69 g, 0.67 mL, 6.0 mmol), gave a 59/41 mixture from which the major diastereoisomer **5a** was isolated by column chromatography over silica gel (eluent: petrol/AcOEt 70:30) in 53% (0.50 g) yield as a yellowish oil: ^{1}H NMR ($CDCl_3$): δ 1.40 (t, 3H, *J*=7.1 Hz, CH_3), 1.94 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.37-4.48 (m, 2H, CH_2), 6.24 (s, 1H, H_2), 6.94 (d, 2H, *J*=8.7 Hz), 7.48 (d, 2H, *J*=8.7 Hz); ^{13}C NMR ($CDCl_3$): δ 13.9 (CH_3CH_2), 19.4 (CH_3), 55.5 (OCH_3), 63.8 (CH_2), 70.2 (C5), 88.6 (C4), 107.6 (C2), 111.0 (CN), 112.1 (CN), 114.3 (C3' and C5'), 129.2 (C2' and C6'), 124.7 (C1'), 161.9 (C4'), 166.2 (C=O); HRMS, *m/z*: 316.1064 found (calcd for $C_{16}H_{16}N_2O_5$, $M^{+\bullet}$ requires: 316.10592). Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.44; H, 5.06; N, 8.53%. The minor diastereoisomer **5b** was identified by NMR: ^{1}H NMR ($CDCl_3$): δ 1.41 (t, 3H, *J*=7.1 Hz, CH_3), 1.97 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.42 (t, 2H, *J*=7.2 Hz, CH_2), 6.44 (s, 1H, H2), 6.95 (d, 2H, *J*=8.7 Hz), 7.43 (d, 2H, *J*=8.7 Hz); ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3CH_2), 21.6 (CH_3), 55.5 (OCH_3), 63.8 (CH_2), 71.3 (C5), 88.2 (C4), 108.7 (C2), 111.0 (CN), 111.3 (CN), 114.3 (C3' and C5'), 128.9 (C2' and C6'), 124.8 (C1'), 161.8 (C4'), 167.2 (C=O). The general procedure 2 (285 W, 7 min to reach 180°C and 30 min at 180°C), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.60 g) and ethyl pyruvate (0.35 g, 0.33 mL, 3.0 mmol), gave a 41/59 mixture from which the minor diastereoisomer **5a** was isolated by column chromatography over silica gel (eluent: petrol/AcOEt 70:30) in 38% (0.36 g) yield.

Diastereoisomers of ethyl 5,5-dicyano-2,4-diphenyl-1,3-dioxolane-4-carboxylate (6). The general procedure 1 (reflux of 80 h), using 3-phenyloxirane-2,2-dicarbonitrile (**1a**, 0.51 g) and ethyl phenylglyoxylate (**2b**, 0.53 g, 0.48 mL, 3.0 mmol), gave a 54/46 mixture. The major diastereoisomer **6a** was identified by NMR: ^{1}H NMR ($(CD_3)_2CO$): δ 1.32 (t, 3H, *J*=7.1 Hz, CH_3), 4.42 (q, 2H, *J* = 7.0, CH_2), 6.72 (s, 1H, H2), 7.54-7.83 (m, 10H); ^{13}C NMR ($(CD_3)_2CO$): δ 14.0 (CH_3), 64.9 (CH_2), 72.7 (C5), 92.1 (C4), 108.8 (C2), 111.7 (CN), 113.1 (CN), 126.2 (C2" and C6"), 128.3, 129.8 and 130.2 (C2', C3', C5', C6', C3" and C5"), 131.6 (C4"), 132.0 (C1'), 132.0 (C1"), 134.1 (C4'), 166.3 (C=O). The minor diastereoisomer **6b** was identified by NMR: ^{1}H NMR ($(CD_3)_2CO$): δ 1.18 (t, 3H, *J*=7.1 Hz, CH_3), 4.27 (q, 2H, *J*=7.1 Hz, CH_2), 6.84 (s, 1H, H2), 7.54-7.83 (m, 10H); ^{13}C NMR ($(CD_3)_2CO$): δ 13.9 (CH_3), 64.3 (CH_2), 73.7 (C5), 91.2 (C4), 108.4 (C2), 111.4 (CN), 112.0 (CN), 126.6 (C2" and C6"), 127.9, 129.5 and 130.0 (C2', C3', C5', C6', C3" and C5"), 131.5 (C4"), 131.6 (C4'), 132.1 (C1'), 134.2 (C1"), 166.8 (C=O). HRMS, *m/z*: 275.0819 found (calcd for $C_{17}H_{11}N_2O_2$, $[M\text{-}CO_2Et]^{+\bullet}$ requires: 275.0820) (mixture of **6a** and **6b**). Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 69.21; H, 4.62; N, 8.41% (mixture of **6a** and **6b**).

Diastereoisomers of ethyl 2-(4-chlorophenyl)-5,5-dicyano-4-phenyl-1,3-dioxolane-4-carboxylate (7). The general procedure 1 (reflux of 72 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.61 g) and ethyl phenylglyoxylate (**2b**, 0.53 g, 0.48 mL, 3.0 mmol), gave a 60/40 mixture from which the major diastereoisomer **7a** was isolated by column chromatography over silica gel (eluent: heptane/Et_2O 70:30) followed by crystallization from petrol/Et_2O 4:1 in 52% (0.60

g) yield as a white powder: mp 109 °C; ^{1}H NMR ($(CD_3)_2CO$): δ 1.32 (t, 3H, *J*= 7.1 Hz, CH_3), 4.42 (q, 2H, *J* = 7.1 Hz, CH_2), 6.75 (s, 1H, H2), 7.61-7.64 (m, 5H), 7.73-7.81 (m, 4H); ^{13}C NMR ($(CD_3)_2CO$): δ 14.1 (CH_3), 65.0 (CH_2), 72.7 (C5), 92.2 (C4), 108.0 (C2), 111.6 (CN), 113.1 (CN), 126.3 (C2" and C6"), 129.9, 130.1 and 130.3 (C2', C3', C5', C6', C3" and C5"), 131.8 (C4"), 132.0 (C1'), 133.2 (C1"), 137.6 (C4'), 166.3 (C=O); HRMS, *m/z*: 309.0435 found (calcd for $C_{17}H_{10}N_2O_2{}^{35}Cl$, $[M\text{-}CO_2Et]^{+\bullet}$ requires: 309.0431). Anal. Calcd for $C_{20}H_{15}ClN_2O_4$: C, 62.75; H, 3.95; N, 7.32. Found: C, 62.68; H, 4.02; N, 7.23%. The minor diastereoisomer **7b** was isolated similarly in 18% (0.21 g) yield as a white powder: mp 78 °C; ^{1}H NMR ($(CD_3)_2CO$): δ 1.20 (t, 3H, *J*= 7.1 Hz, CH_3), 4.28 (q, 2H, *J* = 7.1 Hz, CH_2), 6.88 (s, 1H, H2), 7.57-7.62 (m, 5H), 7.75 (d, 2H, *J* = 8.5 Hz, H2' and H6'), 7.80-7.84 (m, 2H); ^{13}C NMR ($(CD_3)_2CO$): δ 13.9 (CH_3), 64.6 (CH_2), 73.8 (C5), 91.4 (C4), 107.8 (C2), 111.4 (CN), 111.9 (CN), 126.8 (C2" and C6"), 129.8, 129.9 and 130.2 (C2', C3', C5', C6', C3" and C5"), 131.7 (C4"), 132.1 (C1'), 133.3 (C1"), 137.2 (C4'), 166.8 (C=O).

Diastereoisomers of ethyl 5,5-dicyano-2-(4-methoxyphenyl)-4-phenyl-1,3-dioxolane-4-carboxylate (8). The general procedure 1 (reflux of 60 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.60 g) and ethyl phenylglyoxylate (**2b**, 0.53 g, 0.48 mL, 3.0 mmol), gave a 38/62 mixture from which the minor diastereoisomer **8a** was identified by NMR: ^{1}H NMR ($(CD_3)_2CO$): δ 1.31 (t, 3H, *J*=7.1 Hz, CH_3), 3.87 (s, 3H, OCH_3), 4.42 (qd, 2H, *J* = 7.1 and 1.1 Hz, CH_2), 6.64 (s, 1H, H2), 7.10 (d, 2H, *J* = 8.7 Hz, H3' and H5'), 7.60-7.68 (m, 5H), 7.77-7.81 (m, 2H); ^{13}C NMR ($(CD_3)_2CO$): δ 14.1 (CH_3), 55.9 (OCH_3), 64.9 (CH_2), 72.7 (C5), 92.0 (C4), 109.1 (C2), 111.9 (CN), 113.4 (CN), 115.2 (C3' and C5'), 126.0 (C1'), 126.3 (C2" and C6"), 130.2 and 130.3 (C2', C6', C3" and C5"), 131.7 (C4"), 132.3 (C1"), 163.0 (C4'), 166.5 (C=O). The major diastereoisomer **8b** was isolated by column chromatography over silica gel (eluent: heptane/Et_2O 70:30) followed by crystallization from petrol/Et_2O 4:1 in 48% (0.54 g) yield as a pale green powder: mp 95 °C; ^{1}H NMR ($(CD_3)_2CO$): δ 1.24 (t, 3H, *J*=7.1 Hz, CH_3), 3.87 (s, 3H, OCH_3), 4.33 (qd, 2H, *J* = 7.1 and 2.3 Hz, CH_2), 6.75 (s, 1H, H2), 7.09 (d, 2H, *J*=8.8 Hz), 7.59-7.68 (m, 5H), 7.77-7.81 (m, 2H); ^{13}C NMR ($(CD_3)_2CO$): δ 14.0 (CH_3), 55.9 (OCH_3), 64.5 (CH_2), 73.8 (C5), 91.2 (C4), 108.9 (C2), 111.6 (CN), 112.3 (CN), 115.0 (C3' and C5'), 130.0 and 130.2 (C2', C6', C3" and C5"), 131.6 (C4"), 132.5 (C1"), 162.8 (C4'), 167.1 (C=O); HRMS, *m/z*: 378.1212 found (calcd for $C_{21}H_{18}N_2O_5$, $M^{+\bullet}$ requires: 378.1216). Anal. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.38; H, 4.73; N, 7.25%.

Diastereoisomers of 5,5-dicyano-2-phenylspiro[1,3-dioxolane-4,3'-indolin-2'-one] (10). The general procedure 1 (reflux of 32 h), using 3-phenyloxirane-2,2-dicarbonitrile (**1a**, 0.51 g) and isatin (**9a**, 0.44 g, 3.0 mmol), gave a 57/43 mixture from which the major diastereoisomer **10a** was isolated by column chromatography over silica gel (eluent: petrol/AcOEt 60:40) in 42% yield as a white powder: mp 160°C; ^{1}H NMR ($(CD_3)_2CO$): δ 6.95 (s, 1H, H2), 7.15 (d, 1H, *J*=7.9 Hz, H7'), 7.25 (t, 1H, *J*=7.6 Hz, H5'), 7.55-7.59 (m, 4H, H6' and Ph), 7.84-7.90 (m, 3H, H4' and Ph), 10.2 (s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$): δ 72.0 (C5), 86.5 (C4), 109.5 (C2), 111.5 (CN), 111.6 (CN), 112.3 (C7'), 122.2 (C8'), 124.0 (C5'), 127.7 (C4'), 129.0 (C3" and C5"), 129.5 (C2" and C6"), 132.0 (C4"), 133.9 (C6'), 134.4 (C1"), 143.8 (C9'), 170.6 (C=O); HRMS, *m/z*: 317.0815 found (calcd for $C_{18}H_{11}N_3O_3$, $M^{+\bullet}$ requires: 317.08004). Anal. Calcd for $C_{18}H_{11}N_3O_3$: C, 68.14; H, 3.49; N, 13.24. Found: C, 68.38; H, 3.53; N, 12.96%. The minor diastereoisomer **10b** was identified by NMR: ^{1}H NMR ($(CD_3)_2CO$): δ 7.13 (s, 1H, H2), 7.15 (d, 1H, *J*=7.9 Hz, H7'), 7.29 (t, 1H, *J*=7.6 Hz, H5'), 7.55-7.59 (m, 4H, H6' and Ph), 7.75-7.90 (m, 3H, H4' and Ph), 10.3 (s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$): δ 70.2 (C5), 88.0 (C4), 109.3 (C2), 112.0 (CN), 112.3 (C7'), 113.0 (CN), 119.1 (C8'), 124.2 (C5'), 127.8 (C4'), 128.3 (C3" and C5"), 129.8 (C2" and C6"), 132.1 (C4"), 133.9 (C6'), 134.0 (C1"), 144.4 (C9'), 172.5 (C=O). The general procedure 2 (285 W, 15 min to reach 180°C and 60 min at 180°C), using 3-phenyloxirane-2,2-dicarbonitrile (**1a**, 0.51 g) and isatin (**9a**, 0.29 g, 2.0 mmol), gave a 55/45 mixture.

Diastereoisomers of 2-(4-chlorophenyl)-5,5-dicyanospiro[1,3-dioxolane-4,3'-indolin-2'-one] (11). The general procedure 1 (reflux of 24 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.61 g) and isatin (**9a**, 0.44 g, 3.0 mmol), gave a 75/25 mixture from which the major diastereoisomer **11a** was isolated by column chromatography over silica gel (eluent: petrol/AcOEt 60:40) in 66% (0.70 g) yield as a white powder: mp 198°C; ^{1}H NMR ($(CD_3)_2CO$): δ 6.97 (s, 1H, H2), 7.15 (d, 1H, *J*=8.0 Hz, H7'), 7.25 (t, 1H, *J*=7.7 Hz, H5'), 7.54 (td, 1H, *J*=7.8 and 1.1 Hz, H6'), 7.58 (d, 2H, *J*=8.5 Hz, H3" and H5"), 7.83 (d, 1H, *J*=7.6 Hz, H4'), 7.91 (d, 2H, *J*=8.5 Hz, H2" and H6"), 10.2 (s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$): δ 72.0 (C5), 86.5 (C4), 108.6 (C2), 111.3 (CN), 111.4 (CN), 112.3 (C7'), 121.8 (C8'), 124.0 (C5'), 127.7 (C4'), 129.7 (C3" and C5"), 130.8 (C2" and C6"), 132.8 (C1"), 133.9 (C6'), 137.5 (C4"), 143.8 (C9'), 170.7 (C=O); HRMS, *m/z*: 351.0405 found (calcd for $C_{18}H_{10}N_3O_3{}^{35}Cl$, $M^{+\bullet}$ requires: 351.04107). Anal. Calcd for $C_{18}H_{10}ClN_3O_3$: C, 61.46; H, 2.87; N, 11.95. Found: C, 61.33; H, 2.86; N, 11.70%. The minor diastereoisomer **11b** was identified by NMR: ^{1}H NMR ($(CD_3)_2CO$): δ 7.13 (s, 1H, H2), 7.16 (d, 1H, *J*=8.0 Hz, H7'), 7.29 (t, 1H, *J*=7.1 Hz, H5'), 7.56-7.64 (m, 3H, H6', H3" and H5"), 7.79-7.85 (m, 3H, H4', H2" and H6"), 10.3 (s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$): δ 71.1 (C5), 88.0 (C4), 108.4 (C2), 112.0 (CN), 112.4 (C7'), 112.9 (CN), 119.1 (C8'), 124.2 (C5'), 127.8 (C4'), 130.0 and 130.1 (C2", C3", C5" and C6"), 132.9 (C1"), 134.5 (C6'), 137.5 (C4"), 144.4 (C9'), 172.3 (C=O). The general procedure 2 (285 W, 15 min to reach 180°C and 50 min at 180°C), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.61 g) and isatin (**9a**, 0.29 g, 2.0 mmol), gave a 54/46 mixture.

Diastereoisomers of 5,5-dicyano-2-(4-methoxyphenyl)spiro[1,3-dioxolane-4,3'-indolin-2'-one] (12). The general procedure 1 (reflux of 14 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.60 g) and isatin (**9a**, 0.44 g, 3.0 mmol), gave a 55/45 mixture from which the major diastereoisomer **12a** was isolated by column

chromatography over silica gel (eluent: petrol/AcOEt 70:30) in 49% (0.51 g) yield as a white powder: mp 188°C; ^{1}H NMR ($(CD_3)_2CO$): δ 3.85 (s, 3H, OCH_3), 6.89 (s, 1H, H2), 7.06 (d, 2H, *J*=8.0 Hz, H3" and H5"), 7.15 (d, 1H, *J*=7.5 Hz, H7'), 7.25 (t, 1H, *J*=7.0 Hz, H5'), 7.54 (t, 1H, *J*=7.1 Hz, H6'), 7.83 (m, 3H, H4', H2" and H6"), 10.2 (s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$): δ 55.7 (OCH_3), 71.9 (C5), 86.3 (C4), 109.7 (C2), 111.6 (CN), 111.8 (CN), 112.3 (C7'), 114.9 (C3" and C5"), 122.3 (C8'), 124.0 (C5'), 125.7 (C1"), 127.7 (C4'), 130.8 (C2" and C6"), 133.8 (C6'), 143.8 (C9'), 162.9 (C4"), 170.9 (C=O); HRMS, *m/z*: 347.0913 found (calcd for $C_{19}H_{13}N_3O_4$, $M^{+\bullet}$ requires: 347.09061). Anal. Calcd for $C_{19}H_{13}N_3O_4$: C, 65.70; H, 3.77; N, 12.10. Found: C, 65.35; H, 3.75; N, 11.78%. The minor diastereoisomer **12b** was identified by NMR: ^{1}H NMR ($(CD_3)_2CO$): δ 3.85 (s, 3H, OCH_3), 7.04-7.30 (m, 4H, H2, H7', H3" and H5"), 7.55-7.88 (m, 5H, H4', H5', H6', H2" and H6"); ^{13}C NMR ($(CD_3)_2CO$): δ 55.6 (OCH_3), 69.9 (C5), 87.6 (C4), 109.5 (C2), 112.1 (CN), 112.3 (C7'), 112.9 (CN), 115.1 (C3" and C5"), 118.9 (C8'), 124.2 (C5'), 125.5 (C1"), 127.8 (C4'), 130.1 (C2" and C6"), 134.1 (C6'), 144.2 (C9'), 162.7 (C4"), 172.4 (C=O). The general procedure 2 (285 W, 5 min to reach 180°C and 30 min at 180°C), 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.60 g) and isatin (**9a**, 0.29 g, 2.0 mmol), gave a 35/65 mixture.

Diastereoisomers of 5,5-dicyano-1'-methyl-2-phenylspiro[1,3-dioxolane-4,3'-indolin-2'-one] (13). The general procedure 1 (reflux of 25 h), using 3-phenyloxirane-2,2-dicarbonitrile (**1a**, 0.51 g) and *N*-methylisatin (**9b**, 0.32 g, 2.0 mmol), gave a 73/27 mixture from which the major diastereoisomer **13a** was isolated by fractional crystallization from petrol/Et_2O 5:1 in 72% (0.48 g) yield as a beige powder: mp 130°C; ^{1}H NMR ($(CD_3)_2CO$): δ 3.33 (s, 3H, CH_3), 6.96 (s, 1H, H2), 7.24 (d, 1H, *J*=7.9 Hz, H7'), 7.30 (td, 1H, *J*=7.7 and 0.79 Hz, H5'), 7.52-7.59 (m, 3H, Ph), 7.63 (td, 1H, *J*=7.9 and 1.1 Hz, H6'), 7.87-7.90 (m, 3H, H4', Ph); ^{13}C NMR ($(CD_3)_2CO$): δ 27.3 (CH_3), 72.0 (C5), 86.2 (C4), 109.6 (C2), 111.0 (C7'), 111.6 (CN), 111.8 (CN), 122.0 (C8'), 124.4 (C5'), 127.3 (C4'), 129.1 (C3" and C5"), 129.6 (C2" and C6"), 132.2 (C4"), 134.0 (C6'), 134.0 (C1"), 145.8 (C9'), 169.2 (C=O); HRMS, *m/z*: 331.0962 found (calcd for $C_{19}H_{13}N_3O_3$, $M^{+\bullet}$ requires: 331.09569). Anal. Calcd for $C_{19}H_{13}N_3O_3$: C, 68.88; H, 3.95; N, 12.68. Found: C, 68.69; H, 4.01; N, 12.34%. The minor diastereoisomer **13b** was identified by NMR: ^{1}H NMR ($(CD_3)_2CO$): δ 3.34 (s, 3H, CH_3), 7.13 (s, 1H, H2), 7.25 (d, 1H, *J*=7.8 Hz, H7'), 7.33 (t, 1H, *J*=7.7 Hz, H5'), 7.54-7.89 (m, 7H, Ph, H6' and H4'); ^{13}C NMR ($(CD_3)_2CO$): δ 27.0 (CH_3), 72.1 (C5), 86.3 (C4), 109.5 (C2), 111.2 (C7'), 112.1 (CN), 113.2 (CN), 121.9 (C8'), 124.8 (C5'), 127.6 (C4'), 128.5 (C3" and C5"), 130.0 (C2" and C6"), 132.3 (C4"), 134.1 (C1"), 134.6 (C6'), 146.4 (C9'), 171.0 (C=O).

Diastereoisomers of 2-(4-chlorophenyl)-5,5-dicyano-1'-methylspiro[1,3-dioxolane-4,3'-indolin-2'-one] (14). The general procedure 1 (reflux of 26 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.61 g) and *N*-methylisatin (**9b**, 0.32 g, 2.0 mmol), gave a 74/26 mixture from which the major diastereoisomer **14a** was isolated by fractional crystallization from petrol/Et_2O 5:1 in 73% (0.53 g) yield as a beige powder: mp 146°C; ^{1}H NMR ($(CD_3)_2CO$): δ 3.33 (s, 3H, CH_3), 6.98 (s, 1H, H2), 7.25 (d, 1H, *J*=7.9 Hz, H7'), 7.30 (td, 1H, *J*=7.7 and 0.74 Hz, H5'), 7.60 (d, 2H, *J*=8.5 Hz, H3" and H5"), 7.63 (td, 1H, *J*=7.9 and 1.1 Hz, H6'), 7.86 (d, 1H, *J*=7.7 Hz, H4'), 7.90 (d, 2H, *J*=8.5 Hz, H2" and H6"); ^{13}C NMR ($(CD_3)_2CO$): δ 27.3 (CH_3), 72.1 (C5), 86.5 (C4), 108.7 (C2), 111.1 (C7'), 111.4 (CN), 111.7 (CN), 121.7 (C8'), 124.4 (C5'), 127.3 (C4'), 129.9 (C3" and C5"), 130.9 (C2" and C6"), 133.0 (C1"), 134.1 (C6'), 137.7 (C4"), 145.9 (C9'), 169.4 (C=O); HRMS, *m/z*: 365.0559 found (calcd for $C_{19}H_{12}N_3O_3{}^{35}Cl$, $M^{+\bullet}$ requires: 365.05672). Anal. Calcd for $C_{19}H_{12}ClN_3O_3$: C, 62.39; H, 3.31; N, 11.49. Found: C, 62.02; H, 3.25; N, 11.17%. The minor diastereoisomer **14b** was identified by NMR: ^{1}H NMR ($(CD_3)_2CO$): δ 3.34 (s, 3H, CH_3), 7.14 (s, 1H, H2), 7.25 (d, 1H, *J*=8.0 Hz, H7'), 7.33 (td, 1H, *J*=7.7 and 0.66 Hz, H5'), 7.61 (d, 2H, *J*=8.6 Hz, H3" and H5"), 7.67 (td, 1H, *J*=7.8 and 1.2 Hz, H6'), 7.80 (d, 2H, *J*=8.5 Hz, H2" and H6"), 7.85 (dd, 1H, *J*=7.6 and 0.45 Hz, H4'); ^{13}C NMR ($(CD_3)_2CO$): δ 27.0 (CH_3), 70.5 (C5), 88.0 (C4), 108.5 (C2), 111.2 (C7'), 111.9 (CN), 113.0 (CN), 118.8 (C8'), 124.7 (C5'), 127.5 (C4'), 130.1 and 130.2 (C2", C3", C5" and C6"), 133.0 (C1"), 134.6 (C6'), 137.7 (C4"), 146.4 (C9'), 171.0 (C=O).

Diastereoisomers of 5,5-dicyano-2-(4-methoxyphenyl)-1'-methylspiro[1,3-dioxolane-4,3'-indolin-2'-one] (15). The general procedure 1 (reflux of 20 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.60 g) and *N*-methylisatin (**9b**, 0.32 g, 2.0 mmol), gave a 63/37 mixture from which the major diastereoisomer **15a** was identified by NMR: ^{1}H NMR ($(CD_3)_2CO$): δ 3.35 (s, 3H, NCH_3), 3.88 (s, 3H, OCH_3), 6.89 (s, 1H, H2), 7.07 (d, 2H, *J*=8.6 Hz, H3" and H5"), 7.21-7.31 (m, 2H, H5' and H7'), 7.59-7.71 (m, 2H, H4' and H6'), 7.82 (d, 2H, *J*=8.7 Hz, H2" and H6"); ^{13}C NMR ($(CD_3)_2CO$): δ 27.2 (NCH_3), 55.8 (OCH_3), 71.2 (C5), 85.9 (C4), 109.7 (C2), 111.0 (C7'), 111.6 (CN), 111.9 (CN), 115.0 (C3" and C5"), 122.1 (C8'), 124.3 (C5'), 125.8 (C1"), 127.3 (C4'), 130.9 (C2" and C6"), 133.9 (C6'), 145.8 (C9'), 163.0 (C4"), 169.5 (C=O). The minor diastereoisomer **15b** was isolated by fractional crystallization from petrol/Et_2O 5:1 in 30% (0.22 g) yield as a white powder: mp 163°C; ^{1}H NMR ($(CD_3)_2CO$): δ 3.33 (s, 3H, NCH_3), 3.87 (s, 3H, OCH_3), 7.08 (s, 1H, H2), 7.09 (d, 2H, *J*=8.6 Hz, H3" and H5"), 7.25 (d, 1H, *J*=7.9 Hz, H7'), 7.33 (t, 1H, *J*=7.7 Hz, H5'), 7.66 (t, 1H, *J*=7.9 Hz, H6'), 7.69 (d, 2H, *J*=8.6 Hz, H2" and H6"), 7.85 (d, 1H, *J*=7.4 Hz, H4'); ^{13}C NMR ($(CD_3)_2CO$): δ 27.0 (NCH_3), 55.9 (OCH_3), 70.4 (C5), 87.8 (C4), 109.7 (C2), 111.1 (C7'), 112.1 (CN), 113.3 (CN), 115.2 (C3" and C5"), 119.1 (C8'), 124.7 (C5'), 125.8 (C1"), 127.5 (C4'), 130.2 (C2" and C6"), 134.5 (C6'), 146.3 (C9'), 163.1 (C4"), 171.2 (C=O); HRMS, *m/z*: 281.1057 found (calcd for $C_{17}H_{15}NO_3$, $[M\text{-}CO(CN)_2]^{+\bullet}$ requires: 281.10519). Anal. Calcd for $C_{20}H_{15}N_3O_4$: C, 66.48; H, 4.18; N, 11.63. Found: C, 66.22; H, 4.10; N, 11.24%.

Diastereoisomers of 5,5-dicyano-2-phenylspiro[1,3-dioxolane-4,3'-(5'-chloroindolin-2'-one)] (16). The general procedure 1 (reflux of 28 h), using 3-phenyloxirane-2,2-dicarbonitrile (**1a**, 0.51 g) and 5-chloroisatin (**9c**, 0.36 g, 2.0 mmol), gave a 59/41 mixture from which the major

diastereoisomer **16a** was isolated by fractional crystallization from CH_2Cl_2 in 52% (0.37 g) yield as a beige powder: mp 234°C; ^{1}H NMR ($(CD_3)_2CO$): δ 7.03 (s, 1H, H2), 7.18 (d, 1H, *J*=8.4 Hz, H7'), 7.53-7.58 (m, 4H, H6', Ph), 7.86-7.94 (m, 3H, H4', Ph), 10.3 (s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$): δ 72.0 (C5), 86.3 (C4), 109.6 (C2), 111.3 (CN), 111.6 (CN), 113.8 (C7'), 124.2 (C8'), 127.8 (C4'), 128.7 (C5'), 129.0 (C3" and C5"), 129.6 (C2" and C6"), 132.1 (C4"), 133.7 (C6'), 133.7 (C1"), 142.7 (C9'), 170.4 (C=O); HRMS, *m/z*: 351.0426 found (calcd for $C_{18}H_{10}N_3O_3{}^{35}Cl$, $M^{+\bullet}$ requires: 351.04107). Anal. Calcd for $C_{18}H_{10}ClN_3O_3$: C, 61.46; H, 2.87; N, 11.95. Found: C, 61.31; H, 2.85; N, 11.82%. The minor diastereoisomer **16b** was isolated similarly in 28% (0.20 g) yield as yellow needles: mp 154°C; ^{1}H NMR ($(CD_3)_2CO$): δ 7.11 (s, 1H, H2), 7.19 (d, 1H, *J*=8.4 Hz, H7'), 7.54-7.60 (m, 4H, H6', Ph), 7.78-7.85 (m, 3H, H4', Ph), 10.4 (s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$): δ 70.3 (C5), 87.7 (C4), 109.6 (C2), 111.9 (CN), 112.9 (CN), 113.9 (C7'), 121.2 (C8'), 127.9 (C4'), 128.5 (C3" and C5"), 129.0 (C5'), 129.8 (C2" and C6"), 132.2 (C4"), 133.7 (C6'), 134.3 (C1"), 143.3 (C9'), 172.2 (C=O). Anal. Calcd for $C_{18}H_{10}ClN_3O_3$: C, 61.46; H, 2.87; N, 11.95. Found: C, 61.75; H, 2.94; N, 11.92%.

Diastereoisomers of 2-(4-chlorophenyl)-5,5-dicyanospiro[1,3-dioxolane-4,3'-(5'-chloroindolin-2'-one)] (17). The general procedure 1 (reflux of 24 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.61 g) and 5-chloroisatin (**9c**, 0.36 g, 2.0 mmol), gave a 71/29 mixture from which the major diastereoisomer **17a** was isolated by fractional crystallization from CH_2Cl_2 in 59% (0.46 g) yield as a beige powder: mp 259°C; ^{1}H NMR ($(CD_3)_2CO$): δ 7.05 (s, 1H, H2), 7.18 (d, 1H, *J*=8.4 Hz, H7'), 7.55-7.61 (m, 3H, H3", H5" and H6'), 7.87-7.91 (m, 3H, H2", H6" and H4'), 10.3 (s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$): δ 72.0 (C5), 86.3 (C4), 108.7 (C2), 111.1 (CN), 111.4 (CN), 113.8 (C7'), 123.9 (C8'), 127.8 (C4'), 128.7 (C5'), 129.8 (C3" and C5"), 130.8 (C2" and C6"), 132.6 (C1"), 133.8 (C6'), 137.7 (C4"), 142.8 (C9'), 170.5 (C=O); HRMS, *m/z*: 385.0029 found (calcd for $C_{18}H_9N_3O_3{}^{35}Cl_2$, $M^{+\bullet}$ requires: 385.0021). Anal. Calcd for $C_{18}H_9Cl_2N_3O_3$: C, 55.98; H, 2.35; N, 10.88. Found: C, 56.27; H, 2.48; N, 10.55%. The minor diastereoisomer **17b** was isolated in 25% (0.19 g) yield as a white powder: mp 229°C; ^{1}H NMR ($(CD_3)_2CO$): δ 7.11 (s, 1H, H2), 7.19 (d, 1H, *J*=8.4 Hz, H7'), 7.59-7.62 (m, 3H, H3", H5" and H6'), 7.82-7.87 (m, 3H, H2", H6" and H4'), 10.4 (s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$): δ 70.3 (C5), 87.7 (C4), 108.6 (C2), 111.7 (CN), 112.8 (CN), 114.0 (C7'), 121.1 (C8'), 127.9 (C4'), 129.0 (C5'), 130.0 and 130.3 (C2", C3", C5" and C6"), 132.6 (C1"), 134.4 (C6'), 137.7 (C4"), 143.3 (C9'), 172.1 (C=O).

Diastereoisomers of 5,5-dicyano-2-(4-methoxyphenyl)spiro[1,3-dioxolane-4,3'-(5'-chloroindolin-2'-one)] (18). The general procedure 1 (reflux of 17 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.60 g) and 5-chloroisatin (**9c**, 0.36 g, 2.0 mmol), gave a 58/42 mixture from which the major diastereoisomer **18a** was isolated by fractional crystallization from CH_2Cl_2 in 49% (0.37 g) yield as a beige powder: mp 216°C; ^{1}H NMR ($(CD_3)_2CO$): δ 3.86 (s, 3H, OCH_3), 6.98 (s, 1H, H2), 7.06-7.19 (m, 3H, H3", H5" and H7'), 7.57 (dd, 1H, *J*=8.6 and 2.1 Hz, H6'), 7.71-7.91 (m, 3H, H2", H6" and 4'), 10.3 (s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$): δ 55.8 (OCH_3), 70.2 (C5), 87.5 (C4), 109.8 (C2), 112.0 (CN), 113.1 (CN), 113.9 (C7'), 115.2 (C3" and C5"), 121.4 (C8'), 125.5 (C1"), 127.9 (C4'), 128.9 (C5'), 130.3 (C2" and C6"), 134.3 (C6'), 143.3 (C9'), 163.1 (C4"), 172.3 (C=O); HRMS, *m/z*: 383.0474 found (calcd for $C_{19}H_{12}N_3O_4{}^{37}Cl$, $M^{+\bullet}$ requires: 383.04868). Anal. Calcd for $C_{19}H_{12}ClN_3O_4$: C, 59.78; H, 3.17; N, 11.01. Found: C, 59.40; H, 3.11; N, 10.65%. The minor diastereoisomer **18b** was identified by NMR: ^{1}H NMR ($(CD_3)_2CO$): δ 3.87 (s, 3H, OCH_3), 7.08 (s, 1H, H2), 7.06-7.10 (m, 3H, H3", H5" and H2), 7.57 (d, 1H, *J*=8.2 Hz, H7'), 7.60 (d, 1H, *J*=8.6 Hz, H6'), 7.81 (d, 2H, *J*=8.8 Hz, H2" and H6"), 7.88 (d, 1H, *J*=1.5 Hz, H4'), 10.3 (s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$): δ 55.7 (OCH_3), 71.8 (C5), 86.0 (C4), 109.8 (C2), 111.4 (CN), 111.7 (CN), 113.7 (C7'), 114.9 (C3" and C5"), 124.2 (C8'), 125.4 (C1"), 127.8 (C4'), 128.6 (C5'), 130.7 (C2" and C6"), 133.6 (C6'), 142.7 (C9'), 162.9 (C4"), 170.6 (C=O).

Crystallography

Single crystals suitable for X-ray diffraction were grown after slow evaporation (several days at room temperature) of solutions of **4a** in $CDCl_3$, **12a** in dibutyl ether, and **7b**, **11a**, **13a**, **14a**, **14b**, **15b**, **16a**, **17a**, **17b** and **18b** in acetone.

The samples were studied with graphite monochromatized $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). Except for **12a**, X-ray diffraction data were collected at *T* = 100(2) K using APEXII Bruker-AXS diffractometer. The structure was solved by direct methods using the SIR97 program,[21] and then refined with full-matrix least-square methods based on F^2 (SHELX-97)[22] with the aid of the WINGX program.[23] All non-hydrogen atoms were refined with anisotropic thermal parameters. H atoms were finally included in their calculated positions. Except N-linked hydrogen that was introduced in the structural model through Fourier difference maps analysis, H atoms were finally included in their calculated positions. Molecular diagrams were generated by ORTEP-3 (version 1.08).[24]

Crystal data for **4a**: $C_{15}H_{13}ClN_2O_4$, M_r = 320.72, triclinic, space group *P*-1, *a* = 7.5107(5), *b* = 10.4161(8), *c* = 10.9534(7) Å, α = 111.597(3), β = 96.849(3), γ = 103.339(3)°, *V* = 755.25(9) Å^3, *Z* = 2, ρ_{calcd} = 1.41 g.cm^{-3}, μ = 0.272 mm^{-1}. A final refinement on F^2 with 3361 unique intensities and 199 parameters converged at $\omega R(F^2)$ = 0.1162 (R(F) = 0.0493) for 3060 observed reflections with $I > 2\sigma(I)$.

Crystal data for **7b**: $C_{20}H_{15}ClN_2O_4$, M_r = 382.79, monoclinic, $P2_1/a$, *a* = 8.5421(6), *b* = 26.3062(18), *c* = 8.6602(6) Å, β = 111.132(3)°, *V* = 1815.2(2) Å^3, *Z* = 4, ρ_{calcd} = 1.401 g.cm^{-3}, μ = 0.239 mm^{-1}. A final refinement on F^2 with 4140 unique intensities and 245 parameters converged at $\omega R(F^2)$ = 0.0916 (R(F) = 0.0394) for 3483 observed reflections with $I > 2\sigma(I)$.

Crystal data for **11a**: $C_{18}H_{10}ClN_3O_3$, M_r = 351.74, monoclinic, $P2_1/c$, *a* = 11.4743(11), *b* = 10.6042(12), *c* = 13.0970(14) Å, β = 98.668(5)°, *V* = 1575.4(3) Å^3, *Z* = 4, ρ_{calcd}

= 1.483 g.cm^{-3}, μ = 0.266 mm^{-1}. A final refinement on F^2 with 3596 unique intensities and 229 parameters converged at $\omega R(F^2)$ = 0.0873 (R(F) = 0.0371) for 3325 observed reflections with $I > 2\sigma(I)$.

Crystal data for **13a**: $C_{19}H_{13}N_3O_3$, M_r = 331.32, monoclinic, $P2_1/c$, a = 9.1376(6), b = 9.8479(6), c = 17.8528(13) Å, β = 98.305(4)°, V = 1589.66(18) Å^3, Z = 4, ρ_{calcd} = 1.384 g.cm^{-3}, μ = 0.096 mm^{-1}. A final refinement on F^2 with 3640 unique intensities and 226 parameters converged at $\omega R(F^2)$ = 0.11 (R(F) = 0.0443) for 2892 observed reflections with $I > 2\sigma(I)$.

Crystal data for **14a**: $C_{19}H_{12}ClN_3O_3$, M_r = 365.77, monoclinic, $C2/c$, a = 21.887(2), b = 6.6306(8), c = 23.230(2) Å, β = 90.527(5)°, V = 3371.1(6) Å^3, Z = 8, ρ_{calcd} = 1.441 g.cm^{-3}, μ = 0.252 mm^{-1}. A final refinement on F^2 with 3840 unique intensities and 235 parameters converged at $\omega R(F^2)$ = 0.1118 (R(F) = 0.0451) for 3284 observed reflections with $I > 2\sigma(I)$.

Crystal data for **14b**: $C_{19}H_{12}ClN_3O_3$, M_r = 365.77, triclinic, P-1, a = 9.1044(8), b = 9.8097(8), c = 10.3197(9) Å, α = 76.326(5), β = 69.235(4), γ = 87.179(4)°, V = 836.76(12) Å^3, Z = 2, ρ_{calcd} = 1.452 g.cm^{-3}, μ = 0.253 mm^{-1}. A final refinement on F^2 with 3795 unique intensities and 235 parameters converged at $\omega R(F^2)$ = 0.1141 (R(F) = 0.0415) for 3188 observed reflections with $I > 2\sigma(I)$.

Crystal data for **15b**: $C_{20}H_{15}N_3O_4$, M_r = 361.35, triclinic, P-1, a = 9.0017(12), b = 9.2015(12), c = 11.8723(16) Å, α = 84.823(7), β = 69.598(7), γ = 70.128(6)°, V = 866.4(2) Å^3, Z = 2, ρ_{calcd} = 1.385 g.cm^{-3}, μ = 0.099 mm^{-1}. A final refinement on F^2 with 3934 unique intensities and 244 parameters converged at $\omega R(F^2)$ = 0.13 (R(F) = 0.0519) for 3213 observed reflections with $I > 2\sigma(I)$.

Crystal data for **16a**: $C_{18}H_{10}ClN_3O_3$, M_r = 351.74, triclinic, P-1, a = 7.4444(5), b = 8.6287(6), c = 12.8065(8) Å, α = 71.202(3), β = 87.399(3), γ = 83.872(3)°, V = 774.25(9) Å^3, Z = 2, ρ_{calcd} = 1.509 g.cm^{-3}, μ = 0.271 mm^{-1}. A final refinement on F^2 with 3524 unique intensities and 229 parameters converged at $\omega R(F^2)$ = 0.0917 (R(F) = 0.038) for 3302 observed reflections with $I > 2\sigma(I)$.

Crystal data for **17a**: $C_{18}H_9Cl_2N_3O_3$, M_r = 386.18, triclinic, P-1, a = 7.2738(8), b = 9.1406(9), c = 12.8097(14) Å, α = 72.904(4), β = 87.391(4), γ = 83.669(4)°, V = 809.00(15) Å^3, Z = 2, ρ_{calcd} = 1.585 g.cm^{-3}, μ = 0.426 mm^{-1}. A final refinement on F^2 with 3529 unique intensities and 238 parameters converged at $\omega R(F^2)$ = 0.0691 (R(F) = 0.0282) for 3146 observed reflections with $I > 2\sigma(I)$.

Crystal data for **17b**: $C_{18}H_8Cl_2N_3O_3$, M_r = 444.26, monoclinic, $P2_1/n$, a = 13.2556(6), b = 6.9193(3), c = 22.4721(10) Å, β = 95.608(2)°, V = 2051.26(16) Å^3, Z = 4, ρ_{calcd} = 1.439 g.cm^{-3}, μ = 0.35 mm^{-1}. A final refinement on F^2 with 4692 unique intensities and 276 parameters converged at $\omega R(F^2)$ = 0.0784 (R(F) = 0.0349) for 4579 observed reflections with $I > 2\sigma(I)$.

Crystal data for **18b**: $C_{19}H_{12}ClN_3O_4$, M_r = 381.77, monoclinic, $P2_1/n$, a = 7.1149(11), b = 18.630(3), c = 13.388(2) Å, β = 98.387(6)°, V = 1755.6(5) Å^3, Z = 4, ρ_{calcd} = 1.444 g.cm^{-3}, μ = 0.249 mm^{-1}. A final refinement on F^2 with 4026 unique intensities and 248 parameters converged at $\omega R(F^2)$ = 0.1876 (R(F) = 0.0682) for 3013 observed reflections with $I > 2\sigma(I)$.

X-ray diffraction data of **12a** (0.32∗0.15∗0.07 mm) were collected at T = 295(1) K using Oxford Diffraction Xcalibur Saphir 3 diffractometer. $C_{19}H_{13}N_3O_4$, M_r = 347.32, monoclinic, $P2_1/c$, a = 11.989(2), b = 10.720(1), c = 13.132(1) Å, β = 98.847(9)°, V = 1667.6(3) Å^3, Z = 4, ρ_{calcd} = 1.383 g.cm^{-3}, μ = 1.00 cm^{-1}, F(000) = 720. The data collection gave 13272 reflections, and 4892 independent reflections from which 1178 with $I > 2\sigma(I)$.

Computational methods

DFT calculations were carried out using the B3LYP[25] exchange-correlation functionals, together with the standard 6-31G* basis set.[26] This level of theory has been shown suitable to provide enough good performance in the analysis of both geometric and electronic properties in cycloaddition reactions.[19b] The optimizations were carried out using the Berny analytical gradient optimization method.[27] Free energies were calculated with the standard statistical thermodynamics[26] at 383.95 K and 1 atm, and were scaled by a factor of 0.96. Solvent effects, toluene, were considered at the thermodynamic calculations using a self-consistent reaction field (SCRF)[28] based on the polarizable continuum model (PCM) of the Tomasi's group.[29] The electronic structures of stationary points were analyzed by the NBO method.[30] All calculations were carried out with the Gaussian 03 suite of programs.[31]

The ω index[32] is given by the following expression, $\omega = \mu^2/(2\eta)$, in terms of the electronic chemical potential μ and the chemical hardness η.[33] Both quantities may be approached in terms of the HOMO and LUMO energies as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$.[33] Fukui functions[34] condensed to atoms have been evaluated from single point calculations performed at the ground state of molecules at the same level of theory, using a method described elsewhere.[35]

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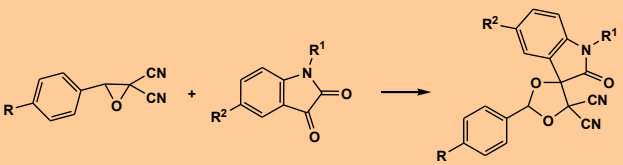

The [3+2] polar cycloaddition reaction between electrophilically activated carbonyl ylides and isatins was investigated. The molecular mechanism was studied using DFT calculations.